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CLINICAL REVIEWS

Pharmacologic Therapy for the Irritable Bowel Syndrome

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ABSTRACT

The management of the irritable bowel syndrome (IBS) remains unsatisfactory. For abdominal pain, antispasmodics are, at best, of only modest efficacy. Tricyclic antidepressants in low dose are useful (with the number needed to treat being three), but side effects and patient concerns regarding use of a centrally acting agent for depression remain limitations. Selective serotonin reuptake inhibitors are of uncertain efficacy in IBS. Opioid agonists, especially loperamide, are useful for diarrhea but not for pain in IBS; rebound constipation also remains a problem. Bile salt sequestering agents are not of established value in IBS but seem to be useful clinically in a small group of IBS patients with diarrhea. Aloestron, a $5HT_3$ antagonist, should be reserved, if available, for women with severe diarrhea predominant IBS who have failed to respond to conventional therapy, and started at a low dose. Fiber and bulking agents may help constipation in some trials, but the evidence that they are efficacious in IBS is equivocal; they are frequently prescribed as first-line drugs for IBS regardless of the primary bowel disturbance but often increase bloating, gas, and pain. Laxatives are not of established value in IBS but are often taken by patients with constipation predominant IBS. Tegaserod, a partial $5HT_4$ agonist, is now available in the United States and other countries for use in women with IBS whose primary bowel symptom is constipation; its efficacy in men and in those with alternating bowel habits is unknown. Probiotics are of uncertain efficacy. Chinese herbal medicine data are insufficient. Other new drugs in development include the cholecystokinin antagonists and novel visceral analgesics. Both current and potential therapies for IBS are reviewed in this article. (Am J Gastroenterol 2003;98: 750–758. © 2003 by Am. Coll. of Gastroenterology)

INTRODUCTION

The irritable bowel syndrome (IBS) is a symptom complex that is characterized by abdominal pain, disturbed defecation, and often bloating (1, 2). A clinically based classification ("Rome") has been developed that is largely based on epidemiological and factor analysis studies combined with clinical experience; however, the exact spectrum of the disorder is still disputed (2). The pathophysiology is actively being explored with increasing evidence for both genetic and environmental contributions (3–5). A subset of patients develops IBS postcolonic infection, with symptoms persisting despite disappearance of the organism; minor inflammatory abnormalities may also persist (4–7). Enterochromaffin cells that contain serotonin may be increased and release abnormal amounts of this neurotransmitter in a subset with IBS, in turn disturbing peristalsis and sensory signaling (7). Abnormal central nervous system processing of afferent signals may be key in some patients, and disturbed central circuits influencing gut motor and sensory pathways may determine the exact symptomatology experienced (8–10).

The subdivision of IBS into types based on predominant bowel pattern remains controversial (2). This is because an uncertain number of patients will fluctuate, and this seems not to be predictable. Moreover, current methods of defining IBS bowel habit subgroups are arbitrary. However, pharmaceutical companies have adopted the classification, as many drugs tend to alter bowel habit in one direction, and this therapeutic effect has been harnessed in attempts to develop new options for IBS. Keys to successful management of IBS include strong reassurance and sensible advice. An explanation of the nature and benign prognosis in terms the patient can understand seems useful. Referral to a local patient support group should be considered. Drug therapy for IBS is currently still unsatisfactory and may often add little to placebo (11, 12). The placebo response is high; it has ranged from 30% to 80% in short term trials, and recent studies suggest that the placebo response can actually increase over a 12-month period when patients are intensively monitored (13). Here, available treatments will be reviewed, followed by a consideration of compounds in development and their current status.

CURRENT THERAPIES

Abdominal Pain in IBS

ANTISPASMODICS. Abdominal pain is a major symptom in IBS, and in the United States anticholinergics (dicyclomine, propantheline, belladona, and hyoscyamine) remain a mainstay of therapy. A recent meta-analysis of 23 randomized trials in IBS concluded that antispasmodics were superior to placebo in terms of global symptom improvement as well as abdominal pain and distension, but not constipa-

Table 1. Antispasmodic Agents for IBS

Medication	Drug Class
Cimetropium bromide*	Antimuscarinic
Pinaverium bromide*	Quaternary ammonium derivative with calcium channel blocking action
Trimebutine*	Peripheral opiate agonist
Mebeverine*	Smooth muscle relaxant, derivative of phenylethylamine; nonanticholinergic
Hyoscyamine	Anticholinergic
Tincture of belladonna	Anticholinergic
Dicyclomine	Anticholinergic
Propanthcline	Anticholinergic

* Not available in the United States.

tion (14). However, the anticholinergic hyoscyamine in various combinations (as well as other antispasmodics including mebeverine, trimebutine, and pinaverium, which are not available in the United States) (Table 1) failed to significantly improve pain (14). Dicyclomine has only been tested at high doses in one low quality trial, and anticholinergic side effects were problematic (15). The studies included were generally of short duration (<8 wk). As the quality of many of the included trials remains questionable (12), the benefit of antispasmodics is probably at best very modest. Indeed, in clinical practice they seem to be most useful for intermittent predictable episodes of postprandial pain, but often fail to relieve the symptom complex. It is not established that sublingual or suppository preparations are advantageous over oral ingestion in terms of onset of action. Many patients are intolerant of these agents because they exacerbate constipation and cause dry mouth. Publication bias has not been excluded as an explanation for the apparent benefit of this drug class in meta-analyses.

ANTIDEPRESSANTS. Tricyclic antidepressants in low doses may be efficacious in IBS over placebo, based on a recent meta-analysis (16). The effect size was also clinically significant (with the number needed to treat being three), and in practice this class of drugs seems particularly useful. The mechanism of action may be central analgesia; tricyclics may take at least 4 wk to become efficacious. However, it seems that many clinicians are reluctant to try these drugs because of perceived patient concerns about using a centrally acting agent. Furthermore, whether the benefit is similar in those with or without psychiatric disturbance is unclear, and the quality of most of the trials was suboptimal (12). Tricyclic antidepressants tend to be constipating and, therefore, one would postulate that they should be of most benefit in diarrhea and deleterious in constipation predominant IBS. Whether the underlying bowel pattern is predictive of treatment success remains unknown. Side effects are a limitation; anticholinergic effects, weight gain, cardiac toxicity, and hematological abnormalities can limit their use.

Selective serotonin reuptake inhibitors (SSRIs) have only been subject to few placebo-controlled studies, and adequate data are lacking. A crossover trial of 14 patients with IBS was positive (17). On the other hand, a parallel group trial of 40 patients failed to detect a benefit over placebo, except for pain although it may have been underpowered (18). Creed et al. found that paroxetine and psychotherapy were superior to usual care in severe IBS in terms of improved quality of life but not abdominal pain (19). It is unclear whether SSRIs would be most useful in constipation predominant IBS (because diarrhea is sometimes a side effect). Other troublesome side effects include nausea, headache, restlessness, anxiety, sweating, and sexual dysfunction.

MISCELLANEOUS AGENTS. Anticonvulsants are of uncertain value in IBS but have analgesic properties. Phenytoin relaxes colonic smooth muscle but was not superior to placebo in one trial (20). β-Blockers may theoretically inhibit colonic motor function, but both atenolol and timolol were not superior to placebos in small trials of patients with IBS (21).

Leuprolide is a gonadotrophin-releasing hormone analog that induces chemical castration. In two small randomized, controlled trials in menstruating women, leuprolide depot injections were superior to placebo in terms of reducing abdominal pain and nausea. However, patients did not fulfill current criteria for IBS, and significant side effects occurred in one half of the patients (22, 23).

Constipation Predominant IBS

FIBER AND LAXATIVES. Fiber and bulking agents are commonly prescribed for IBS. However, clinical trials support only limited benefit for constipation and not other symptoms, although many clinicians prescribe these regardless of the bowel pattern (1, 2). Meta-analyses have concluded that there is insufficient evidence to support a benefit over placebo (11, 12). They are, however, safe and can be prescribed as a placebo (remembering that the placebo response is substantial and that prescription of a placebo is ethical if the patient is informed). Bloating, gas, and pain may be aggravated by bulking agents; therefore, they should be introduced initially in small doses and increased slowly. They may be least useful in patients in whom pain and bloating are the most bothersome symptoms.

Other laxatives are of uncertain benefit in constipation predominant IBS (12). Osmotic laxatives and nonabsorbable carbohydrates often, in practice, aggravate other IBS symptoms, especially bloating. PEG is useful in resistant constipation and, as it is not hydrolyzed by colonic bacteria, may be more effective and cause less bloating (24). Unfortunately, there are no controlled trials in IBS. Stimulant laxatives can cause cramping and do not seem to relieve the IBS symptom complex even if constipation improves. However, no trials in IBS have been conducted. The association of currently available stimulant laxatives with either neoplastic change or enteric nerve damage in humans is not well established, and safety concerns with longer term use in terms of a cathartic colon have very likely been exaggerated (25).

Table 2. Efficacy of Tegaserod in Constipation Predominant IBS, Based on Four Randomized Controlled Trials (Month 3, Primary Endpoint)

	B301 (n = 881)		B307 (Dose Tritation) (n = 841)		B351 (n = 799)		B358 (Females Only) (n = 1519)	
Dosage	Response Rate (%)	Therapeutic Gain (%)	Response Rate (%)	Therapeutic Gain (%)	Response Rate (%)	Therapeutic Gain (%)	Response Rate (%)	Therapeutic Gain (%)
4 mg/day								
Both sexes	38.8	9.1*	38.3	0.8	38.9	6		
Women	38	10.2*	39	1.5	41	8.8		
12 mg/day								
Both sexes	38.4	8.3*	42.2	6	45.7	12.4*		
Women	39	11.3*	43	5.2	46.9	14.8*	43.5	5.3*
Placebo								
Both sexes	30.2		37		33.3			
Women	28		38		32		38.8	

* $p < 0.05$.

SEROTONIN TYPE 4 ($5HT_4$) AGONISTS. The pharmacology of serotonin receptor agents has recently been reviewed in detail elsewhere (26). The substituted benzamides probably act via $5HT_4$ receptors. Cisapride is a 5-HT_4 agonist, although it also has partial 5-HT_3 antagonist actions (26, 27). Cisapride is known to accelerate gastric emptying and to enhance gastric accommodation, but it has less action on the colon in humans (26). Its role in IBS is equivocal based on the available trials (28–30), and it has been withdrawn from use because of rare cardiac toxicity (prolonged QT interval and sudden death).

Tegaserod, a new indole carboxaldehyde derivative, is a partial 5-HT_4 receptor agonist with high potency and specificity (31). Tegaserod has a high affinity for the $5HT_4$ receptor. The intrinsic activity of tegaserod is approximately 21% of serotonin's affinity in the guinea pig ileum, hence the label partial agonist (26). Whether this partial agonist produces less receptor desensitization is unknown. Indeed, whether tachyphylaxis occurs with this drug has not been adequately evaluated, but the 12-wk studies reviewed below did not show evidence for tachyphylaxis (26).

Preclinical studies have observed that tegaserod stimulates the peristaltic reflex, and the effects seemed to be dose dependent with a biphasic response (31). In healthy volunteers, tegaserod has been shown to shorten colonic transit times and to increase the colonic motility index (32). No significant acceleration of colonic transit was observed in 24 female patients with constipation predominant IBS receiving tegaserod 2 mg *b.i.d.*, but proximal colonic filling was significantly accelerated and small bowel transit were modestly accelerated gastric emptying was normal (32). More recent work in 12 healthy male volunteers has demonstrated that tegaserod accelerated gastric emptying and small intestinal transit, and induced a small but significant acceleration of colonic transit (33). It is unclear whether higher doses would have yielded different results in IBS patients. There are promising albeit preliminary data suggesting tegaserod may have visceral analgesic actions in animal models (26, 31).

The efficacy of tegaserod in IBS has been reported in two phase III study published in full (35) and in two other trials (31) (Table 2). In a double-blind, placebo controlled trial (referred to as study 301), 881 patients from Europe with constipation predominant IBS were randomized to 12 wk of therapy after a 4-wk baseline (34). Patients were randomized to placebo or to 2 mg or 6 mg of tegaserod *b.i.d.*. The primary outcome was based on a global assessment; responders were defined as either considerably or completely relieved at least 50% of the time or somewhat relieved 100% of the time in the last 4 wk of the trial. Patients were classified as nonresponders if laxatives were taken. The responder rates overall were 39% and 38% for the 2 mg and 6 mg doses, respectively, compared with 30% for placebo, which was a statistically significant therapeutic gain. Unadjusted responder rates were higher, and indeed it could be argued that the unadjusted results are more appropriate and interpretable in terms of an intention-to-treat analysis. The weekly data show more impressive and arguably more realistic responder rates, because some patients fluctuated in and out of being responders (Fig 1). Stool frequency increased and stool consistency decreased within the week 1 with tegaserod but stabilized by week 2. Although bowel symptoms significantly improved, the efficacy of tegaserod was inconsistent for bloating although there was a positive trend in favor of the drug. A trial of similar size of patients with constipation predominant IBS from the United States reported consistent findings (study 351) but the endpoint was revised, albeit before the blind was broken (Table 2) (31). In an unusual up titration and dose ranging trial (study 307), tegaserod failed to demonstrate superiority to placebo (31). A 1519-patient, 3-month trial confined to women with constipation predominant IBS (study 358) detected a therapeutic gain over placebo in terms of global relief of 13% at month 1 but only 5% at the end of the trial because of an increase in the placebo response; symptoms returned when the drug was ceased supporting clinically significant efficacy (35).

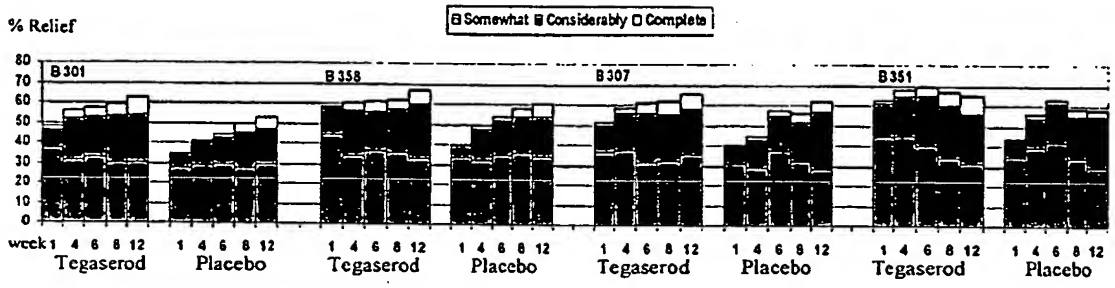

Figure 1. Proportion of patients with complete, considerable or somewhat relief of global IBS symptoms with tegaserod, a $5HT_4$ partial agonist in the four major randomized controlled trials at week 1, 4, 6, 8, and 12. The adjusted results (by intention-to-treat) for the Subject's Global Assessment of relief is presented. Data on file at Novartis Pharmaceuticals, East Hanover, New Jersey.

Tegaserod has convincing, albeit modest efficacy and is well tolerated. A safety concern was raised regarding a small albeit nonsignificant increased incidence of abdominal surgery (tegaserod 0.3% *vs* placebo 0.2%) and cholecystectomy (0.17% *vs* 0.06%, respectively), but this seems very unlikely to be causal. The most common side effect is transient loose stool and headache. Major diarrhea has not been a common problem in practice; it is unknown if this improves with dosage reduction. No cardiac toxicity has been observed. The drug is contraindicated in moderate to severe hepatic impairment and with severe renal failure; although the Food and Drug Administration has mandated the drug is also contraindicated in those with abdominal adhesions, past bowel obstruction or biliary tract disease, these concerns are not based on evidence.

Hence, tegaserod is useful for IBS patients with constipation. The drug seems, in a fluctuating disease, to reduce the number of bad symptom weeks. The drug can be prescribed first line; but trials testing the drug in alternating bowel habit, and as intermittent therapy and in men, remain needed to understand its exact place in management. Although the design of intermittent treatment studies will be particularly challenging, the results would enhance clinical practice strategies.

MISCELLANEOUS AGENTS. Colchicine is an alkaloid that increases spontaneous bowel movements as well as decreasing colonic transit time (36). However, its role in IBS has not been formally explored. Side effects are uncommon, but neuromyopathy and multiorgan failure have been reported and hence the drug must be used with caution (37). The prostaglandin E_1 analog misprostil may have a role in refractory constipation caused by IBS, in part via augmentation of postprandial colonic motility and secretion (38), but there are no controlled trials in IBS. Motor stimulating drugs of the motilin agonist class (*e.g.*, erythromycin, ABT-229) seem to predominantly have their affects in the stomach rather than the colon and are unlikely to be of benefit in IBS (39).

Diarrhea Predominant IBS

NONSPECIFIC ANTIDIARRHEA AGENTS. For diarrhea, the opioid agonists diphenoxylate or loperamide are useful first-line drugs. These agents slow GI transit via effects on circular and longitudinal muscle as well as increasing luminal water absorption and decreasing secretion (40). Loperamide, a butyramide derivative, is advantageous over diphenoxylate as it does not have opioid activity with standard dosing, and may also increase rectal tone (41). Codeine phosphate should generally be avoided because of the high risk of inducing dependence. Randomized controlled trials with loperamide have only demonstrated a benefit for diarrhea rather than pain (12) and rebound constipation is a clinical problem. They are most useful as prophylactic agents to prevent predictable episodes of diarrhea on waking, eating, traveling, or while under stress.

The relevance of bile acid malabsorption and the value of bile salt sequestrants in IBS have not been carefully evaluated in randomized trials, but anecdotal data suggest cholestryamine may be of value (42). Bismuth subsalicylate is available over the counter but it has not been evaluated as an antidiarrheal agent in IBS. Moreover, use should only be intermittent as bismuth accumulation and toxicity including encephalopathy remains a concern with prolonged exposure.

SEROTONIN TYPE 3 ($5HT_3$) ANTAGONISTS. Ondansetron was the first $5HT_3$ antagonist to be evaluated in terms of actions on the gut in health and IBS (43–47). The drug has been shown to slow colonic and orocecal transit in normal subjects (43, 44). In diarrhea predominant IBS, it slowed colonic transit and improved stool consistency but not stool weight (47). No benefit on abdominal pain was demonstrated in IBS, although the study was underpowered (47).

Alosetron is a highly selective 5-HT_3 antagonist that is substantially more potent than ondansetron (26). Alosetron has been shown to increase jejunal basal fluid and electrolyte absorption (48). In male rats undergoing repeated colorectal distension, FOS like immunoreactivity (Fos-L1) in the spinal cord increased and this was inhibited by alosetron (49). However, there is no direct evidence that alosetron in humans alters visceral hypersensitivity. In IBS, the drug relaxed the left colon and in turn resulted in reduced perception of volume distension but did not affect pressure

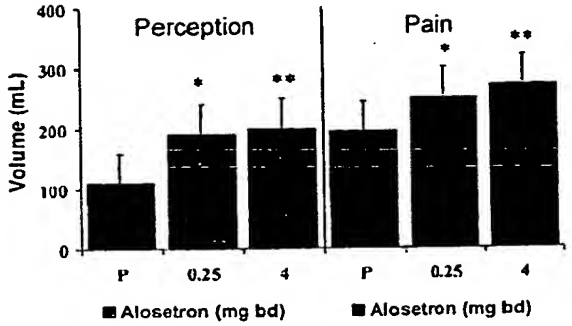

Figure 2. Changes in volume perception with alosetron *versus* placebo in the colon as measured by a barostat balloon. Note that alosetron did not alter pressure perception and that changes in volume reflect colonic relaxation. From Ref. 50, with permission.

distension sensory thresholds (Fig. 2) (50). Alosetron has been demonstrated to slow colonic (and in particular ascending colon) transit in patients with IBS (51). More interestingly, at least in murine isolated small bowel, alosetron selectively inhibited the migrating motor complex and this was induced in female mice at a lower concentration than in males (52). The drug does not seem to be anxiolytic in humans (26).

In one phase III trial, female patients with IBS were randomized to alosetron 1 mg *b.i.d.* (n = 324) or placebo (n = 323) (53); a modest but convincing therapeutic gain in terms of a global assessment measure (labeled adequate relief) was observed during the 12 wk of therapy with alosetron (Fig. 3) (53). Stool frequency and consistency, and urgency also improved. Similar results were demonstrated in other trials (54, 55). Alosetron was compared with mebeverine in a head to head trial in 623 nonconstipated female IBS patients (56). A significant benefit of alosetron over mebeverine was identified by week 4 and was generally maintained over the 3-month period, but symptoms returned to baseline when the drug was ceased (Fig. 3). There was no placebo group included so it is unclear whether mebeverine was more efficacious than placebo in this trial. Alosetron was of no value for bloating in the trials. Recently, efficacy in men was described in a preliminary report but seemed to be less than in women (57).

Alosetron was voluntarily withdrawn by the company in November, 2000, but was reapproved by the FDA in June, 2002. Availability is on a limited basis, with a recommendation to start at a dose of 1 mg daily; only 1 mg *b.i.d.* was tested in the phase III trials (58). There were multiple isolated case reports of ischemic colitis and severe constipation linked to drug use. Ischemic colitis was rare and mild but affected approximately one in 700–1,000 patients receiving the drug, and occurred in nonelderly patients with no other risk factors (58, 59). Severe constipation requiring surgery necessitating colectomy or inducing perforation was rare, but affected approximately one in 10,000 cases taking alosetron (26, 58). Among this group in the United States, there were a small number of deaths reported that were possibly drug related (26, 58). Its use, therefore, must be restricted for the moment to women with severe and resistant diarrhea predominant IBS who do not alternate to constipation; those with very loose stools and urgency probably respond best to this drug class.

SOMATOSTATIN. Somatostatin analogues may be useful for pain and severe diarrhea in IBS because they modulate sensory afferents as well as slow transit (60, 61). However, their side effects (including gallstone formation) and the currant lack of an oral preparation are limitations. Moreover, no adequate clinical trials have been conducted in IBS.

Bloating in IBS

Gas bloat in IBS remains a symptom complex that is very poorly treated with current therapy. Fiber and bulking agents may aggravate the problem (62). There is no evi-

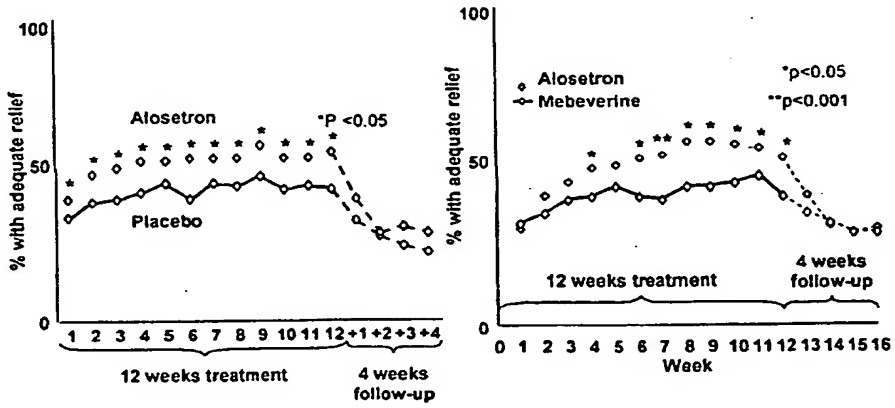

Figure 3. Proportion of IBS patients with adequate relief of abdominal pain and discomfort from two trials of alosetron, a $5HT_3$ antagonist. From Refs. 53 and 56, with permission.

dence that simethicone works in IBS, and trials of charcoal have been equivocal or negative (63). Prokinetics are also not yet of established value, but more data are needed (12, 34). Trials of probiotics have been equivocal, but there are small positive studies in particular with *Lactobacillus plantarum* in terms of relief of abdominal pain and global symptoms (64–66). α-Galactosidase (which digests glucose linkages in complex carbohydrates) reduces flatus but probably little else (67). Antibiotics have been claimed to reduce symptoms of IBS, but the study designs have been suboptimal and the data unconvincing (68–70). Impaired gas expulsion may be a key underlying mechanism in IBS; neostigmine can promote gas excretion but increases abdominal pain and is too toxic for routine use (71). Malodorous flatus may possibly respond to zinc acetate, bismuth subsalicylate, or a bulky charcoal cushion device placed outside the rectum (63, 72). Chinese herbal medicine was judged possibly useful based on one high quality trial (73).

POTENTIAL FUTURE THERAPIES

Drugs for Abdominal Pain in IBS

The quest to develop new antispasmodics continues. However, gut selective muscarinic M3 antagonists including zamifenacin and darifenacin have been disappointing in IBS (26, 74). β_3-Agonists are motor-inhibiting drugs, but their role in IBS remains unclear (75).

κ-Opioid agonists do not modulate motility but reduce sensory signaling; fedotozine, a κ-opioid agonist with modest selectivity, reduced hypersensitivity to colonic distensions in IBS patients (76). However, fedotozine demonstrated only a minor benefit in IBS (albeit statistically significant) over placebo in one randomized trial (77). This drug is no longer being evaluated. However, other more selective κ-opioid agonists are under consideration. Tachykinin receptor antagonists (including NK_1 and NK_2 antagonists) may theoretically be visceral analgesics as well as antispasmodics (78). A neurokinin 1 antagonist (TAK 637) has been evaluated in phase II clinical trials in IBS (79), but no published trial data are available and work seems to have ceased. Gabapentin derivatives are analgesic anticonvulsants that are being evaluated in IBS, but no data are available.

Drugs for Constipation Predominant IBS

OTHER SEROTONIN TYPE 4 ($5HT_4$) AGONISTS. Prucalopride is a benzofurancarboxamide. It is a selective and potent 5-HT_4 receptor agonist that has been tested in idiopathic chronic constipation (80). In two phase II trials comprising 1226 patients with chronic constipation, 2 and 4 mg of prucalopride significantly increased the proportion who reported three or more spontaneous stools weekly *versus* placebo (81). Prucalopride has not been studied in IBS. Intestinal carcinogenicity in animals and cardiac toxicity, however, have been potential concerns.

A number of other compounds have been developed that are 5-HT_4 receptor agonists. Norcisapride, a metabolite of cisapride, was in clinical trials but is likely to have little distal gut action, and cardiac toxicity has also been observed (26). Mosapride, a $5HT_4$ agonist/5HT3 antagonist, has not been tested in IBS (82). Renzapride (AZM-112) is also a $5HT_4$ agonist with $5HT_3$ antagonist activity that is in clinical trials for IBS. Other $5HT_4$ agonists with $5HT_3$ antagonist activity include ML-1035 and E3620 (82). Whether a combination of actions on serotonin receptors would be useful in IBS is as yet unclear, but cisapride was not impressive in its efficacy (28–30).

SEROTONIN TYPE 3 ($5HT_3$) AGONISTS. The $5HT_3$ agonist MKC-733 accelerated small bowel transit in healthy subjects in a preliminary report (83). This indicates the drug class may have a role in constipation predominant IBS, but there are no trial data.

CHOLECYSTOKININ ANTAGONISTS. Cholecystokinin (CCK) antagonists may modulate colonic transit in both health and constipation (27, 82). In a trial of dexloxiglumide, a CCK_1 antagonist, 129 IBS patients were randomized to 200 mg *t.i.d.* daily or placebo for 12 wk. In those who had constipation predominant IBS, a significant albeit modest benefit was obtained with dexloxiglumide in a subgroup analysis (84). Another preliminary report looked less promising; but in a subgroup analysis, women with constipation may have had a better response to the drug (85). The development of gallstones secondary to reduced gallbladder contractility may theoretically be a side effect of CCK_1 antagonism, but this has not been observed in the studies to date.

OPIOID ANTAGONISTS. A recent trial of an oral formulation of naloxone suggested this drug could have modest efficacy in constipation-predominant IBS but this remains to be established (86).

Drugs for Diarrhea Predominant IBS

OTHER SEROTONIN TYPE 3 ($5HT_3$) ANTAGONISTS. Cilansetron has *in vitro* properties similar to those of alosetron and is currently in trials for IBS (26). An initial study reported that cilanstron was superior to placebo in IBS with diarrhea, and surprisingly the efficacy was similar in men and women in contrast to the alosetron trials (87). Granisetron was demonstrated to increase perceptual volume thresholds in the rectum in IBS but does not have established visceral analgesic actions (26). Other $5HT_3$ antagonists including tropisetron (ICS 205–930), which also is a $5HT_4$ antagonist, and YM-114; they have not been tested in IBS (26). It is unknown whether ischemic colitis is a class effect or an idiosyncratic side effect of alosetron. However, there has also been one possible case of ischemic colitis with cilansetron (26).

SEROTONIN TYPE 4 ($5HT_4$) ANTAGONISTS. 5-HT_4 antagonists theoretically may be antidiarrheal and antinoci-

ceptive. Piboserod was in phase II trials; sulamserod is in phase I trials (26). In health, piboserod (SB-207266) in doses that antagonized the effects of the 5-HT_4 agonist cisapride, only slightly delayed colonic transit (and this was not significant) (88). Moreover, disappointingly piboserod did not alter small bowel transit, and did not change colonic sensation or motor activity (88). Hence, a role in diarrhea predominant IBS has not been documented.

α_2 AGONISTS. Clonidine, an α_2 receptor agonist, enhanced rectal compliance and reduced fasting colonic motor activity (89); it may therefore be efficacious in IBS associated with rectal urgency or feelings of incomplete evacuation, as was alosetron (53–55). However, the α_2 agonist lidamidine was not superior to placebo in two trials (90, 91). More work is ongoing evaluating this drug class.

ALTERNATIVE TREATMENT APPROACHES

A number of exotic approaches have been considered, with as yet unconvincing outcomes. Replacement of colonic flora has been tested in uncontrolled trials but the efficacy and safety is not established, and cannot be condoned outside randomized trials (92). The local action of antibiotics suppressing colonic flora may be beneficial in some patients, but requires more rigorous testing (67–69). Certain probiotics may help reduce some of the symptoms of IBS, especially flatulence (63–65). Peppermint oil may be of some value in IBS but the evidence is not convincing (93, 94). Chinese herbal medicine was shown to produce a significant improvement of global IBS symptoms in one trial, but a combination of herbs was given, the truly active agents remain unknown and the results require confirmation (72). Acupuncture is of uncertain benefit (95). Psychological therapies are useful but the trials have generally not been optimal, and arguably the efficacy in terms of symptom relief is modest; indeed, assessment of symptom relief based on rigorous outcome measures has been lacking (96).

CONCLUSIONS

New drugs for IBS are needed, as currently available agents provide generally suboptimal results. Some novel receptor agents show promising results; but these are directed at improving symptoms in a subset of IBS patients, and no panacea has been discovered. Additional knowledge about mechanisms should eventually lead to breakthroughs in therapy; however, if IBS is a true neurological bowel disease, then this will continue to be challenging (97). At this point in time, physicians still need to rely on a holistic approach including reassurance and explanation, plus judicious use of drugs to control major symptoms during exacerbations.

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REFERENCES

1. Drossman DA, Camilleri M, Mayer EA, Whitehead WE, Camilleri MI. AGA technical review on irritable bowel syndrome. Gastroenterology 2002;123:2108–31.
2. Drossman DA, Corazziari E, Talley NJ, et al. eds. Rome II. The functional gastrointestinal disorders. McLean, VA: Degnon, 2000.
3. Morris-Yates AD, Talley NJ, Boyce P, et al. Evidence of a genetic contribution to functional bowel disorder. Am J Gastroenterol 1998;93:1311–7.
4. Gwee KA, Graham JC, McKendrick NW, et al. Psychometric scores and persistence of irritable bowel after infectious diarrhoea. Lancet 1996;347:150–3.
5. Gwee KA, Leong VL, Graham C, et al. The role of psychological and biological factors in postinfective gut dysfunction. Gut 1999;44:400–6.
6. Talley NJ, Butterfield J. Mast cell infiltration and degranulation in colonic mucosa in the irritable bowel syndrome. Am J Gastroenterol 1996;91:1675–6.
7. Spiller RC, Jenkins D, Thornley JP, et al. Increased rectal mucosal entero-endocrine cells, T lymphocytes, and increased gut permeability following acute Campylobacter enteritis and in post-dysenteric irritable bowel syndrome. Gut 2000;47:804–11.
8. Munakata J, Naliboff B, Harraf F, et al. Repetitive sigmoid stimulation induces rectal hyperalgesia in patients with irritable bowel syndrome. Gastroenterology 1997;112:55–63.
9. Mertz H, Morgan V, Tanner G, et al. Regional cerebral activation in irritable bowel syndrome and control subjects with painful and non-painful rectal distension. Gastroenterology 2000;118:842–8.
10. Kim D-Y, Camilleri M. Serotonin. A mediator of the brain-gut connection. Am J Gastroenterol 2000;95:2698–709.
11. Akehurst R, Kaltenthaler E. Treatment of irritable bowel syndrome: A review of randomised controlled trials. Gut 2001;48:272–82.
12. Jailwala J, Imperiale TF, Kroenke K. Pharmacologic treatment of the irritable bowel syndrome: A systematic review of randomized, controlled trials. Ann Intern Med 2000;133:136–47.
13. Nothcutt AR, Mangel AW, Hamm LR, et al. Persistent placebo response during a year-long controlled trial of IBS treatment. Gastroenterology 2001;120:A640.
14. Poynard T, Regimbeau C, Benhamou Y. Meta-analysis of smooth muscle relaxants in the treatment of irritable bowel syndrome. Aliment Pharmacol Ther 2001;15:355–61.
15. Page JG, Dimberger GM. Treatment of the irritable bowel syndrome with Bentyl (dicyclomine hydrochloride). J Clin Gastroenterol 1981;3:153–6.
16. Jackson JL, O'Malley PG, Tomplans G, et al. Treatment of functional gastrointestinal disorders with anti-depressant medications: A meta-analysis. Am J Med 2000;108:65–72.
17. Broekaert D, Vos R, Gevers AM, et al. A double-blind randomized placebo-controlled crossover trial of citalopram, a selective serotonin reuptake inhibitor, in irritable bowel syndrome. Gastroenterology 2001;120:A641.
18. Kuiken SD, Burgres P, Tytgat GNJ. Fluoxetine (Prozac) for the treatment of irritable bowel syndrome: A randomized, controlled clinical trial. Gastroenterology 2002;122:A-551.
19. Creed F, Fernandes L, Guthrie E, et al. The cost-effectiveness of psychotherapy and paroxetine for severe irritable bowel syndrome. Gastroenterology 2003;124:303–17.
20. Greenbaum DS, Ferguson RK, Kater LA, et al. A controlled therapeutic study of the irritable bowel syndrome: Effect of diphenylhydantoin. N Engl J Med 1973;288:13–6.
21. McIntyre AS, Burnham WR, Thompson DG. Atenolol in irritable bowel syndrome. Lancet 1998;85756:67.

22. Mathias JR, Clench MH, Abell TL, et al. Effect of leuprolide acetate in treatment of abdominal pain and nausea in premenopausal women with functional bowel disease: A double-blind, placebo-controlled, randomized study. Dig Dis Sci 1998;43: 1347–55.
23. Mathias JR, Clench MH, Reeves-Darby VG, et al. Effect of leuprolide acetate in patients with moderate to severe functional bowel disease. Double-blind, placebo-controlled study. Dig Dis Sci 1994;39:1155–62.
24. Cleveland MV, Flavin DP, Ruben RA, et al. New polyethylene glycol laxative for treatment of constipation in adults: A randomized, double-blind, placebo-controlled study. South Med J 2001;94:478–81.
25. Xing JH, Soffer EE. Adverse effects of laxatives. Dis Colon Rectum 2001;44:1201–9.
26. Talley NJ. New drug classes: Neuroenteric modulators for the irritable bowel syndrome. Lancet 2001;358:2061–8.
27. Talley NJ. Review article: 5-Hydroxytryptamine agonists and antagonists in the modulation of gastrointestinal motility and sensation. Aliment Pharmacol Ther 1992;6:273–89.
28. Schutze K, Brandstatter G, Dragogsics B, et al. Double-blind study of the effect of cisapride on constipation and abdominal discomfort as components of the irritable bowel syndrome. Aliment Pharmacol Ther 1997;11:387–94.
29. Noor W, Small PK, Loudon MA, et al. Effects of cisapride on symptoms and postcibal small-bowel motor function in patients with irritable bowel syndrome. Scand J Gastroenterol 1998;33:601–11.
30. Farup PG, Hovdenak N, Wetterhus S, et al. The symptomatic effect of cisapride in patients with irritable bowel syndrome and constipation. Scand J Gastroenterol 1998;33:128–31.
31. Camilleri M. Tegaserod. Aliment Pharmacol Ther 2001;15: 277–89 (review article).
32. Prather CM, Camilleri M, Zinsmeister AR, et al. Tegaserod accelerates corocecal transit in patients with constipation-predominant irritable bowel syndrome. Gastroenterology 2000; 118:463–8.
33. Degen L, Matzinger D, Merz M, et al. Tegaserod, a 5HT4 receptor partial agonist, accelerates gastric emptying and gastrointestinal transit in healthy male subjects. Aliment Pharmacol Ther 2001;15:1745–51.
34. Mueller-Lissner S, Fumagalli I, Bardhan KD, et al. Tegaserod, a 5HT4 receptor partial agonist, relieves symptoms in irritable bowel syndrome patients with abdominal pain, bloating and constipation. Aliment Pharmacol Ther 2001;15:1655–66.
35. Novick J, Miner P, Krause R, Glebas K, Bliesath H, Ligozio G, Ruegg P, Lefkowitz M. A randomized, double-blind, placebo-controlled trial of tegaserod in female patients suffering from irritale bowel syndrome with constipation. Aliment Pharmacol Ther 2002;16:1877–88.
36. Berne GN, Eaker EY, Davis RH, Sninsky CA. Colchicine is an effective treatment for patients with chronic constipation: An open-label trial. Dig Dis Sci 1997;42:1959–63.
37. Abraham SC, Yardley JH, Wu TT, et al. Colchicine toxicity: Distinct morphological findings in gastrointestinal biopsies. Am J Surg Pathol 2001;25:1067–73.
38. Roarty TP, Weber F, Soykan I, McCallum RW. Misoprostol in the treatment of chronic refractory constipation: Results of a long-term open label trial. Aliment Pharmacol Ther 1997;11: 1059–66.
39. Talley NJ, Verlinden M, Snape W, et al. Failure of a motilin receptor agonist (ABT-229) to relieve symptoms of functional dyspepsia in patients with and without delayed gastric emptying: A randomized double blind placebo controlled trial. Aliment Pharmacol Ther 2001;4:1653–61.
40. Cann PA, Read NW, Holdsworth CD, Barends D. Role of loperamide and placebo in management of irritable bowel syndrome (IBS). Dig Dis Sci 1984;29:239–47.
41. Hallgren T, Fath S, Delbro DS, et al. Loperamide improves and sphincter function and continence after restorative proctocolectomy. Dig Dis Sci 1994;39:2612–18.
42. Smith MJ, Cherian P, Raju GS, et al. Bile acid malabsorption in persistent diarrhoea. J R Coll Physicians Lond 2000;34: 448–51.
43. Talley NJ, Phillips SF, Haddad A, et al. GR 38032F (Ondansetron), a selective 5-HT 3 receptor antagonist, slows colonic transit in healthy man. Dig Dis Sci 1990;35:477–80.
44. Talley NJ, Phillips SF, Haddad A, et al. Effect of selective serotonin 5-HT_3 antagonist (GR38032F) on small intestinal transit and release of gastrointestinal peptides. Dig Dis Sci 1989;34:1511–5.
45. Hammer J, Phillips SF, Talley NJ, et al. Effect of a 5HT-3 antagonist (ondansetron) on rectal sensitivity and compliance in health and the irritable bowel syndrome. Aliment Pharmacol Ther 1993;7:543–51.
46. Zighelboim J, Talley NJ, Phillips SF, et al. Visceral perception in irritable bowel syndrome. Rectal and gastric responses to distension and serotonin type 3 antagonism. Dig Dis Sci 1995; 40:819–27.
47. Steadman CJ, Talley NJ, Philips SF, et al. Selective 5-HT_3 receptor antagonism with ondansetron as treatment for diarrhea-predominant irritable bowel syndrome. A pilot study. Mayo Clinic Proc 1992;67:732–8.
48. Bearcroft CP, Andrea EA, Farthing MJ. In vivo effects of 5-HT_3 antagonist alosetron on basal and cholera toxin-induced secretion in the human jejunum: A segmental perfusion study. Aliment Pharmacol Ther 1997;11:1109–14.
49. Kozlowsk CM, Green A, Grundy D, et al. The 5-HT_3 receptor antagonist alosetron inhibits the colorectal distension induced depressor response and spinal c-fos expression in the anaesthetized rat. Gut 2000;46:474–80.
50. Delvaux M, Louvel D, Mamet JP, et al. Effect of alosetron on responses to colonic distension in patients with irritable bowel syndrome. Aliment Pharmacol Ther 1998;12:849–55.
51. Houghton LA, Foster JM, Whorwell PJ. Alosetron, a 5-HT_3 receptor antagonist, delays colonic transit in patients with irritable bowel syndrome and healthy volunteers. Aliment Pharmacol Ther 2000;14:775–82.
52. Bush TG, Spencer NJ, Sanders KM, Smith TK. Effects of alosctron on spontaneous migrating motor complexes in murine small and large intestine in vitro. Am J Physiol Gastrointest Liver Physiol 2001;281:G974–83.
53. Camilleri M, Northcutt AR, Kong S, et al. Efficacy and safety of alosetron in women with irritable bowel syndrome: A randomised, placebo-controlled trial. Lancet 2000;355:1035–40.
54. Camilleri M, Chey WY, Mayer EA, et al. A randomized controlled clinical trial of the serotonin type 3 receptor antagonist alosetron in women with diarrhea-predominant irritable bowel syndrome. Arch Intern Med 2001;161:1733–40.
55. Lembo T, Wright RA, Bayby B, et al. Alosetron controls bowel urgency and provides global symptom improvement in women with diarrhea-predominant irritable bowel syndrome. Am J Gastroenterol 2001;96:2662–70.
56. Jones RH, Holtmann G, Rodrigo L, et al. Alosetron relieves pain and improves bowel function compared with mebeverin in female nonconstipated irritable bowel syndrome patients. Aliment Pharmacol Ther 1999;13:1419–27.
57. Edwards EB, Heitman CK, Hall P, et al. A twelve-week, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, phase II study to assess the clinical efficacy of alosetron (GR68755) in male subjects with irritable bowel

syndrome. Am J Gastroenterol 2001;96(suppl):S317 (abstract).
58. Hyman PE, Garvey TQ. Return of alosetron. Exp Opin Drug Safety 2002;1:1–4.
59. Fridel D, Thomas R, Fischer RS. Ischemic colitis during treatment with alosetron. Gastroenterology 2001;120:557–60.
60. Talley NJ, Turner I, Middleton WR. Somatostatin and symptomatic relief of irritable bowel syndrome. Lancet 1987;8568: 1144.
61. Bradette M, Delvaux M, Staumot G, et al. Octreotide increases thresholds of colonic visceral perception in IBS patients without modifying muscle tone. Dig Dis Sci 1994;39:1171–8.
62. Francis CY, Whorwell PJ. Bran and irritable bowel syndrome: Time for reappraisal. Lancet 1994;344:39–40.
63. Fink RN, Lembo AJ. Intestinal gas. Curr Treatment Options Gastroenterol 2001;4:333–7.
64. Nobaek S, Johansson MI, Molin G, et al. Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome. Am J Gastroenterol 2000;95:1231–8.
65. Niedzielin K, Kordecki H, Birkenfeld B. A controlled, double-blind, randomized study on the efficacy of Lactobacillus plantarum in patients with irritable bowel syndrome. Eur J Gastroenterol Hepatol 2001;13:1143–7.
66. Quigley E, O'Mahony L, McCarthy J, et al. Probiotics for the irritable bowel syndrome (IBS): A randomized, double-blind, placebo-controlled comparison of lactobacillus and bifidobacterium strains. Gastroenterology 2002;122:A59.
67. Ganiats TG, Norcross WA, Halverson AI, et al. Does Beano prevent gas? A double-blind, crossover study of oral alpha-galactosidase to treat dietary oligosaccharide intolerance. J Fam Pract 1994;39:441–5.
68. Pimental M, Chang M, Lin HC. Eradication of small intestinal bacterial overgrowth reduces symptoms of irritable bowel syndrome. Am J Gastroenterol 2000;95:3503–6.
69. Pimental M, Chow E, Lin HC. Neomycin leads to a dramatic improvement in IBS symptoms that depend on lactulose breath testing findings: A double blind randomized placebo controlled study. Gastroenterology 2002;122:A60.
70. Moayyedi P, Sduffett S, Mason S, et al. The influence of antibiotics on irritable bowel syndrome: A randomised controlled trial. Gastroenterology 2002;122:A465.
71. Serra J, Azpiroz F, Malagelada JR. Impaired transit and tolerance of intestinal gas in the irritable bowel syndrome. Gut 2001;48:14–9.
72. Suarez FL, Spingfield J, Levitt MD. Identification of gases responsible for the odour of human flatus and evaluation of a device purported to reduce this odour. Gut 1998;43:1004.
73. Bensoussan A, Talley NJ, Hing M, et al. Treatment of irritable bowel syndrome with Chinese herbal medicine. A randomized controlled trial. JAMA 1998;18:1585–89.
74. Houghton LA, Rogers J, Whorwell PJ, et al. Zamifenacin (UK-76, 654) a potent gut M3 selective muscarinic antagonist, reduces colonic motor activity in patients with irritable bowel syndrome. Aliment Pharmacol Ther 1997;11:561–8.
75. Lipworth BJ. Clinical pharmacology of beta3-adrenoreceptors. Br J Clin Pharmacol 1996;42:291–300.
76. Delvaux M, Louvel D, Lagier E, et al. The kappa agonist fedotozine relieves hypersensitivity to colonic distension in patients with irritable bowel syndrome. Gastroenterology 1999;116:3845.
77. Dapoigny M, Abitbol JL, Fraitag B. Efficacy of peripheral kappa agonist fedotozine versus placebo in treatment of IBS. A multicenter dose response study. Dig Dis Sci 1995;40: 2244–9.
78. Patacchini R, Maggi CA. Peripheral tachykinin receptors as targets for new drugs. Eur J Pharmacol 2001;429:13–21.
79. Kamo I, Imai S, Okanishi S, Doi T. Possible site of action of TAK-637, a tachykinin NK(1) receptor antagonist, on the micturition reflex in guinea pigs. Eur J Pharmacol 2000;401: 235–40.
80. Bouras EP, Camilleri M, Burton DD, et al. Prucalopride accelerate gastrointestinal and colonic transit in patients with constipation without a rectal evacuation disorder. Gastroenterology 2001;120:354–60.
81. Johanson JF, Miner PB, Parkman HI, et al. Prucalopride (PRU) improves bowel movement (BM) frequency and symptoms (Sx) in patients (PATIENTS) with chronic constipation (CC). Results of two double-blind placebo-controlled trials. Gastroenterology 2000;118:A175.
82. Scarpignato C, Pelosini I. Management of irritable bowel syndrome: Novel approaches to the pharmacology of gut motility. Can J Gastroenterol 1999;13(suppl):50–65A.
83. Coleman N, Marciani L, Blackshaw PE, et al. MKC733, a 5HT3 receptor agonist, stimulates small bowel transit and relaxes the gastric fundus in man. Gut 2001;48(suppl 1):A44.
84. D'Amato M, Labum RR, Whorwell PJ, et al. The CCKa receptor-antagonist dexloxiglumide in the treatment of IBS. Gastroenterology 1999;116:A981.
85. D'Amato M, Whorwell PJ, Thompson DG, et al. The CCK1 receptor antagonist dexloxiglumide is effective and safe in female patients with diarrhea-predominant irritable bowel syndrome. Am J Gastroenterol 2001;96(suppl):S317 (abstract).
86. Hawkes ND, Rhodes J, Evans BK, Rhodes P, Hawthorne AB, Thomas GA. Nalaxone treatment for irritable bowel syndrome–a randomized controlled trial with an oral formulation. Aliment Pharmacol Ther 2002;16:1649–54.
87. Caras S, Krause G, Biesheuvel E, Steinborn C. Cilansetron shows efficacy in male and female non-constipated patients with irritable bowel syndrome in a United States study. Gastroenterology 2001;120:A1139.
88. Bharucha AE, Camilleri M, Haydock S, et al. Effects of a serotonin 5HT 4 receptor antagonist SB-207266 on gastrointestinal motor and sensory function in humans. Gut 2000;47: 667–74.
89. Malcolm A, Camilleri M, Kost L, et al. Towards identifying optimal doses for alpha 2 adrenergic modulation of colonic and rectal motor and sensory function. Aliment Pharmacol Ther 2000;14:783–93.
90. Prior A, Wilson KM, Whorwell PJ. Double-blind study of an alpha 2 agonist in the treatment of the irritable bowel syndrome. Aliment Pharmacol Ther 1988;2:535–9.
91. Awad RA, Llorens F, Camelo AL, Sanchez M. A randomized double-blind placebo-controlled trial of lidamidine HCL in irritable bowel syndrome. Act Gastroenterol Latinoam 2000; 30:169–75.
92. Borody T, George L, Andrews P, et al. Bowel flora alteration: A potential cure for inflammatory bowel disease and irritable bowel syndrome? Med J Aust 1989;150:604.
93. Pittler MH, Ernst E. Peppermint oil for irritable bowel syndrome: A critical review and metaaanalysis. Am J Gastroenterol 1998;93:1131–5.
94. Liu JH, Chen GH, Yeh HZ, et al. Enteric coated peppermint-oil capsules in the treatment of irritable bowel syndrome: A prospective, randomized trial. Gastroenterology 1997;32:765–8.
95. Fireman Z, Segal A, Kopelman Y, et al. Acupuncture treatment for irritable bowel syndrome: A double-blind controlled study. Digestion 2001;64:100–3.
96. Talley NJ, Owen BK, Boyce P, Paterson K. Psychological treatment for irritable bowel syndrome: A critique of controlled treatment trials. Am J Gastroenterol 1996;91:277–86.
97. Talley NJ, Spiller R. Irritable bowel syndrome: A little understood organic bowel disease? (Invited Seminar). Lancet 2002; 360:555–64.